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DOES RIFAMPICIN INCREASE SERUM LEVELS OF TESTOSTERONE AND OESTRADIOL BY INDUCING SEX HORMONE BINDING GLOBULIN CAPACITY?

In a recent study we found that a 2 week course of the antibiotic rifampicin in eight male volunteers reduced by 70% serum levels of 25-hydroxyvitamin D (25-OHD), the major circulating metabolite of the vitamin (Brodie *et al.*, 1980). As there was concomitant induction of hepatic monooxygenase activity, as evidenced by significant increases in the hydroxylation of antipyrine and cortisol, it seems possible that induction of vitamin D wastage pathways explained the fall in 25-OHD. As testosterone and oestradiol are also endogenous substrates for the hepatic monooxygenase system (Gustafsson & Ingelman-Sundberg, 1975), we have investigated the possibility that the levels of these hormones are altered by rifampicin treatment, using sera stored from our previous study. As both are bound in plasma to sex hormone binding globulin (SHBG) (Iqbal &

Johnson, 1977) the binding capacity of this carrier protein was also measured.

Eight healthy male subjects, aged 29–35 years, took rifampicin 600 mg daily for 2 weeks. Serum samples were obtained at the beginning of the study (week 0), on the day following cessation of rifampicin treatment (week +2) and 2 weeks after the last rifampicin dose (week +4). All blood samples were centrifuged immediately and the sera stored at -20°C until analysis. Serum testosterone and oestradiol were measured by radioimmunoassay (Kjeld, Puah & Joplin, 1976) and SHBG binding capacity by affinity chromatography (Iqbal & Johnson, 1977). All samples were run in a single assay. Statistical analysis was by Student's *t*-test for paired values. The results are shown in Table 1. All subjects showed a rise in serum testosterone after 2 weeks treatment with

Table 1 Effect of treatment with rifampicin on serum testosterone, oestradiol and sex hormone binding globulin (SHBG) levels in eight male subjects (mean $\pm$ s.d.). Rifampicin was taken from week 0 to +2.

Assay	Normal range in males	Week 0	Week +2	Week +4
Testosterone (nmol l ⁻¹)	10–28	24.5 $\pm$ 5.7	35.9*** $\pm$ 7.4	27.8 $\pm$ 6.8
Oestradiol (pmol l ⁻¹)	<150	128 $\pm$ 9	127 $\pm$ 5	268** $\pm$ 140
SHBG (nmol DHT bound l ⁻¹)	20–40	27.5 $\pm$ 4.5	40.5** $\pm$ 6.1	32.6* $\pm$ 4.1

P* < 0.05, *P* < 0.01, ****P* < 0.001

DHT = 5 α -dihydroxytestosterone

rifampicin ($P < 0.001$) and the values returned to baseline within 2 weeks of stopping the drug. Serum oestradiol concentrations were not significantly elevated until 2 weeks after the last dose of the drug ($P < 0.01$). At this time, six subjects had oestradiol levels above the upper limit of normal for the assay in males. SHBG binding capacity was also elevated by rifampicin treatment ($P < 0.01$) and although this fell when the drug was discontinued it was still significantly different from baseline 2 weeks later ($P < 0.05$). There were no significant correlations between the changes in either hormone and SHBG binding capacity.

Both testosterone (Rudd, 1976) and oestradiol (Morris, 1976) are synthesised from cholesterol via pregnanolone. This first conversion is catalysed by a mitochondrial cytochrome P-450 dependent monooxygenase system which is thought to be rate limiting in the biosynthesis of these steroid hormones (Butt, 1976). The subsequent metabolism of pregnanolone to testosterone and oestradiol is accomplished in several steps, many of which are catalysed by cytochrome P-450 monooxygenases. Moreover the further metabolism of the two hormones also occurs via such monooxygenases (Gustafsson & Ingelman-Sundberg, 1976; Shiverick & Neims, 1979). Rifampicin is known to induce cytochrome P-450 mediated monooxygenase activity in man (Ohnhaus & Park, 1979; Brodie *et al.*, 1980). Testosterone levels have been shown previously to be elevated during rifampicin treatment and the authors attributed this to induction of testosterone biosynthesis (Nocke-Finck & Breuer, 1980). In addition, metabolism of exogenously administered oestradiol has been shown to be induced by rifampicin both in vivo (Bolt, Bolt &

Kappus, 1977) and by human liver microsomes in vitro (Bolt, Kappus & Bolt, 1975). However, both hormones are bound to SHBG in the plasma and the binding capacity of this carrier protein can be induced by a number of anticonvulsant enzyme-inducing drugs (Victor, Lundberg & Johansson, 1977; Breckenridge *et al.*, 1980). SHBG levels were lower in eight women following cessation of long term rifampicin therapy for tuberculosis (Back *et al.*, 1980). In this study rifampicin has been clearly shown to induce SHBG capacity in males and this provides the likeliest explanation for the rise in testosterone concentration.

Whether these changes in SHBG explain the rise in oestradiol is more arguable as the levels of this hormone were not elevated when the rise in SHBG was maximal. Thus, rifampicin may induce the synthesis of oestradiol. There have been sporadic reports of rifampicin causing gynaecomastia (Mariani, 1968; Van der Muelin, 1974) and it is possible that the rise in circulating oestradiol levels reported in the present study might provide an explanation for this observation.

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MICROSOMAL ENZYME INDUCTION AFTER HALOTHANE ANAESTHESIA

Hepatitis is a rare complication of halothane anaesthesia and the risk is greater with repeated exposure within 28 days (Inman & Mushin, 1978). Minor highly reactive metabolites of the drug are probably responsible for the liver damage and hepatotoxicity in animals occurs only after induction of the microsomal enzymes (Brown & Sipes, 1977). It is possible that halothane anaesthesia itself causes induction of drug metabolizing enzymes thus making hepatotoxicity more likely after a second administration within a few weeks.

Changes in hepatic drug metabolism during the 4 weeks following halothane anaesthesia do not seem to have been investigated in man. We report here the preliminary results of such a study in which the plasma antipyrine half-life was used as an index of drug metabolizing capacity.

The plasma antipyrine half-life was measured on three occasions in five women (mean $\pm$ s.d. age 35.8 $\pm$ 6.6 years) and weight 56.3 $\pm$ 5.6 kg) undergoing lower abdominal hysterectomy under general anaesthesia: (a) the day before surgery, (b) 1 week after, (c) 4 weeks after surgery. None of the patients was taking any medication before the study but one patient smoked 20 cigarettes per day.

All received pethidine 50 mg and promazine 25 mg intramuscularly as premedication and anaesthesia was induced with thiopentone 350 mg. Pancuronium 6 mg was given and the lungs were ventilated with halothane 0.5 or 1% in oxygen 33% and nitrous oxide 66%. Surgery lasted 45-70 min (mean 56.3 $\pm$ 11 min) and neuromuscular blockade was reversed by neostigmine 2.5 mg and atropine 1.2 mg. All received diamorphine 5 mg (7 or 8 doses at 6 hourly intervals) for post-operative pain but none was taking any medication at the times of the studies.

After an overnight fast, each patient received antipyrine 18 mg/kg dissolved in 200 ml of orange

Table 1 Mean antipyrine half-life ($\pm$ s.e. mean), clearance and apparent volume of distribution before and after surgery under general anaesthesia ($n = 5$)

	Pre-operative	1 week	4 weeks
$T_{1/2}$ (h)	12.6 $\pm$ 1.8	8.0 $\pm$ 1.4*	11.6 $\pm$ 1.3
Clearance (ml kg ⁻¹ h ⁻¹)	30.3 $\pm$ 3.6	43.7 $\pm$ 7.7**	33.8 $\pm$ 3.9
Apparent V_d (ml kg ⁻¹)	530 $\pm$ 49	510 $\pm$ 28	541 $\pm$ 46

* $P < 0.01$ compared with preoperative or 4 weeks (paired *t*-test)

** $P < 0.05$ compared with preoperative or 4 weeks (paired *t*-test)

juice. Blood samples were taken at 0, 3, 5, 7, 9 and 12 h and plasma antipyrine concentrations were measured by high performance liquid chromatography (Prescott *et al.*, 1978).

In every patient, the plasma antipyrine half-life was significantly shorter 1 week after surgery (Table 1, Figure 1). Before surgery, the mean antipyrine half-life was within the normal range at 12.5 h (Stevenson, 1977) while 1 week after surgery it was reduced to 8 h ($P < 0.01$) a value similar to that observed in patients taking amylobarbitone chronically (Stevenson 1977). Four weeks after surgery the mean antipyrine half-life had returned almost to normal. Similar changes were found with antipyrine plasma clearance and there was no change in the apparent volume of distribution in the three studies.

Factors influencing antipyrine elimination probably influence also the metabolism of other drugs by cytochrome P450 dependent microsomal enzymes (Stevenson, 1977) although it is not certain whether this applies to halothane. Previous studies of the short